Kidney International, Vol. 22 (1982), pp. 392–397

Nitrogen utilization in uremic patients fed by continuous nasogastric infusion

ELIAS ABRAS and MACKENZIE WALSER

Departments of Pharmacology and Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Nitrogen utilization in uremic patients fed by continuous nasogastric infusion. Patients with severe renal failure were continuously fed an electrolyte-free solution containing oligosaccharides plus 35 g of a mixture of six amino acids and four (or, in one study, five) nitrogen-free analogues via a small-bore nasogastric tube attached to a pump. They also ingested three small meals daily. Total caloric intake averaged 34 kcal/kg (of which 76% was infused). Total nitrogen intake averaged only 3.3 g (of which 68% was infused). Nevertheless, nitrogen balance was positive (average +1.22 g/day). All components of nitrogen excretion fell to unusually low average values: urea nitrogen appearance, 1.14 g/day; non-urea urinary nitrogen, 0.63 g/day; fecal nitrogen, 0.48 g/day. Nitrogen requirement for balance on this regimen, estimated from linear regression, was only 2.0 g/day. Body weight did not change significantly. Serum albumin and transferrin remained normal. Thus, this regimen induces positive nitrogen balance despite low nitrogen intake.

Utilisation de l'azote chez des malades urémiques nourris par une perfusion nasogastrique continue. Des malades ayant une insuffisance rénale sévère ont été nourris de façon continue avec une solution sans électrolytes contenant des oligosaccharides et 35 g d'un mélange de six acides aminés et de quatre (ou, dans une étude, cinq) analogues dépourvus d'azote par une sonde nasogastrique de petit calibre reliée à une pompe. Ils ingéraient également trois petits repas par jour. L'apport calorique total était en moyenne de 34 kcal/kg (dont 76% était perfusé). L'apport total en azote était en moyenne de 3,3 g (dont 68% était perfusé). Néanmoins, le bilan d'azote était positif (en moyenne + 1,22 g/jour). Tous les composants de l'excrétion d'azote se sont abaissés à des valeurs moyennes inhabituellement basses: apparition d'azote dans l'urée 1,14 g/jour; azote urinaire non uréique, 0,63 g/jour; azote fécal, 0,48 g/jour. Les besoins de azote pour l'équilibre avec ce régime, estimés par régression linéaire, étaient de 2,0 g/jour seulement. Le poids corporel n'a pas changé significativement. L'albumine et la transférine sérique sont restées normales. Ainsi ce régime induit un bilan de azote positif malgré un faible apport en azote.

We have recently reported results of two studies in which rats were fed for three weeks by continuous intragastric infusion of a mixture designed to minimize the rate of production of urinary waste products. The principal components of the mixture were sucrose, amino acids, and nitrogen-free analogues of amino acids. In the first study [1], an unusually high efficiency of utilization of nitrogen and minerals was demonstrated; weight gain averaged 3.6 g/day. In the second study [2], rats were infused with a similar mixture, but 90% of each day's urine output was reinfused. Thus renal excretory function was reduced to one tenth of normal. Nevertheless, growth and nitrogen utilization were the same as in nonreinfused rats.

The purpose of the present study was to explore the applicability of this type of nutritional regimen in chronically uremic patients. Continuous enteral alimentation via a small-bore nasogastric tube was employed, but the patients also were given three small meals daily to retain some of the pleasure and social aspects of eating. Food also served as the source of trace metals and essential fats. Sucrose was replaced by oligosaccharides in the infusate so as to reduce the likelihood of inducing diarrhea. A high degree of efficiency of nitrogen utilization was again demonstrated.

Methods

Seven studies of 3 to 10 weeks duration were conducted in four patients (three females and one male), aged 48 to 70 years. The variable duration of the studies was the result of the patients' desires as to length of hospitalization (except for patient 3, who was treated as an outpatient). At least 2 months elapsed between repeat studies in patients 1 and 2. Subjects 1 and 2 had chronic glomerulonephritis. Subject 3 had familial glomerulonephritis. Subject 4 had hypertensive arteriolar nephrosclerosis. Before these studies were initiated as well as between the studies, all but subject 2 were receiving a 20 to 25 g protein diet supplemented by a mixture [3] of essential amino acids and their ketoanalogues; subject 2 was on the same diet without supplements for 8 days. Informed consent was obtained. These studies were approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Subject 1 was studied three times during the course of her illness, subject 2 twice, and the other two patients once each. A silicon rubber tube, size 6.0 French (Keofeed stomach tube, Hedeco Co., Mountain View, California) was inserted into the stomach through the nose without the aid of a guide, by frequent swallowing. The position of the tube was checked radiographically. The tube was replaced with a new one at least once a fortnight. Three of the four patients eventually learned to insert the tube without assistance. The tube was connected to a constant infusion pump. The composition of the infusate is shown in Table 1. The sources and preparation of the amino acids and analogues are given elsewhere [1]. The mixture of amino acids and analogues was prepared and stored at 4° C. Oligosaccharides, added on the day of use, were given as Mor-Rex (Grain Processing Corporation, Muscatine, Iowa), a par-

Received for publication September 14, 1981
and in revised form February 22, 1982

0085–2538/82/0022–0392 $01.20

Table 1. Composition of mixture infused nasogastrically

Mixture	g/day	g N/day
Basic amino acids		
Ornithine	3.60	0.76
Histidine	1.44	0.39
Lysine	3.11	0.60
Neutral amino acids		
Threonine	1.54	0.18
Tryptophan	0.96	0.13
Tyrosine	1.00	0.08
Isoleucine	2.40	0.26
Nitrogen-free analogues		
α-ketoisocaproic acid	7.68	—
α-ketoisovaleric acid	6.72	—
(D,L)-α-hydroxy-γ-methylthiobutyric acid	2.88	—
Phenylpyruvic acid	3.66	—
Total	*34.99*	*2.40*
Oligosaccharides	400 to 500	
Water *q.s.*	1200 to 1400 ml	

tially hydrolyzed cornstarch preparation with a dextrose equivalent of 10. Analysis showed that it contained 0.3 mg of nitrogen and 1.0 mg of sodium per gram. The final mixture had a pH of 2.5.

The mixture used in the first study and one fourth of the second study in patient 1 differed from the others in that R,S-α-keto-β-methylvaleric acid was used instead of L-isoleucine. Plasma isoleucine became depressed instead of rising, and alloisoleucine levels increased markedly. Although neither ill effects nor deterioration of nitrogen balance resulted, isoleucine itself was used, beginning 10 days after the start of the second study in patient 1, and in all of the other studies.

Oligosaccharide intake was varied in response to the patients' oral intake to maintain total caloric intake close to 34 kcal/kg.

The patients were permitted unlimited quantities of the same diet they were ingesting previously, namely a diet that would contain 20 to 25 g of protein of unselected quality and adequate calories, if taken without supplements. This resulted in the ingestion of an average of 8.7 kcal/kg of food, containing an average of 1.17 g of nitrogen. Pyridoxine, 50 mg daily, and a tablet containing B vitamins and ascorbic acid (Larobec) was administered daily. All patients required varying amounts of sodium bicarbonate to prevent acidosis. Neither potassium-binding resins nor aluminum-containing antacids were given except in patient 3, who received 4 g of $Al(OH)_3$ daily.

The infusion rate was begun at one fourth of the full rate on the first day, one half on the second day, three fourths on the third (and sometimes fourth) day, and at the full rate thereafter. Preliminary studies in other patients had shown that administration of the infusion at the full rate from the first day resulted in diarrhea.

On 5 study days in three of the patients, vomiting occurred. These days are omitted from balance periods. Although the tube invariably was ejected during these episodes, no choking resulted. The patients were all ambulatory and were encouraged to walk with the pump attached to a ring stand. On frequent occasions, they were permitted to remove the tube for brief periods to allow greater freedom. As noted below, one patient used a portable pump.

Nitrogen balances during tube-feeding were measured as previously described [4], and also in two patients (1 and 4) in control periods while on the oral ketoacid/amino acid supplement [3]. In each nasogastric feeding study two or three balance periods were obtained between the second and fourth weeks. Continuous 24-hr urine sample collections were made and refrigerated as collected. Stools were collected in 3- to 5-day intervals. Stool markers were not used. No correction was made for skin loss of nitrogen, nor for the amount of nitrogen contained in the oligosaccharide preparation (about 150 mg/day).

Blood samples for chemical analyses were obtained daily. Plasma for amino acid analysis was obtained at least once a week at 8 A.M. before breakfast. Plasma amino acids were measured by automated ion exchange chromatography. All patients were given an injection of ^{14}C-urea to measure body dry weight [5].

Results

Caloric intake. An attempt was made to adjust the oligosaccharide content of the infusate in response to the patients' voluntary food intake so that total caloric intake met energy requirements. Average caloric intake during 15 observation periods in the seven studies was 34.32 kcal/kg (Table 2). However, total caloric intake varied considerably between studies. For example, patient 2 ate well during her first study but had no appetite during her second study a few months later, by which time renal failure had become more severe. Infused calories therefore were increased. Total caloric intake in this patient varied from 34.6 to 44.7 kcal/kg. The fraction of total caloric intake provided as infusate varied from 55 to 100% (average 76%).

Nitrogen balance. As shown in Table 2, nitrogen intake from the infusate averaged 2.17 g/day. Nitrogen intake as protein in food averaged 1.17 g/day. Thus total nitrogen intake averaged 3.34 g/day.

Urea nitrogen appearance, measured as the sum of urea nitrogen excretion and the rate of change of the body pool of urea nitrogen, averaged 1.14 g/day. Plasma urea nitrogen fell to a nadir that averaged 49 mg/dl in the seven studies, despite a 24-hr urea clearance averaging only 1.8 ml/min. The time course of average serum urea nitrogen during nasogastric feeding is shown in Figure 1.

Non-urea urinary nitrogen averaged 0.63 g/day (of this, an average of 0.12 g nitrogen/day was urinary protein). Fecal nitrogen averaged 0.48 g/day. Both of these values are substantially lower than we [4] or others have observed previously in patients with chronic renal failure.

Nitrogen balance was positive in all but one of the 15 periods of observation and was correlated closely ($r = +0.85$, $P < 0.01$) with nitrogen intake (Fig. 2). Balance remains significantly positive if an allowance of 0.35 g/day is made for the difference between nitrogen ingested in the oligosaccharides and unmeasured losses of nitrogen. The intersection of the regression line with the zero nitrogen balance line gives the estimated required nitrogen intake for balance on this regimen, 2.0 g/day (2.3 g/day if corrected as above). Observations in two of these patients on

Table 2. Results of nitrogen balance measurements

						Nitrogen, *g/day*						
			Calories/kg/day			Intake						
Patient no.	Study no.	Balance period no.	TF	PO	*Total*	TF	PO	*Total*	NUUN	Urea N App	Fecal N	b_N
1	1	1	24.81	8.75	*33.56*	1.98	1.13	*3.11*	0.42	1.00	0.61	+1.41
		2	23.48	9.38	*32.86*	1.79	1.30	*3.09*	0.82	1.12	0.77	+0.42
	2	1	23.13	8.72	*31.85*	1.87	1.08	*2.93*	0.45	1.23	0.43	+0.80
		2	21.40	8.89	*30.29*	2.09	1.55	*3.59*	0.67	2.57	0.42	+0.67
	3	1	18.12	7.79	*25.91*	1.56	0.89	*2.45*	0.47	0.62	0.45	+0.90
		2	20.93	6.51	*27.44*	2.07	0.87	*2.94*	0.42	0.89	0.40	+1.18
2	1	1	26.01	14.19	*40.20*	2.20	1.78	*3.98*	0.44	1.32	0.55	+1.89
		2	29.19	15.51	*44.70*	2.13	1.82	*3.95*	0.65	2.18	0.50	+0.86
	2	1	39.83	0.47	*40.29*	2.41	0.00	*2.41*	0.67	1.03	0.23	+0.50
		2	34.00	0.60	*34.60*	1.94	0.06	*2.0*	0.69	0.74	0.28	+0.42
		3	38.32	0.00	*38.32*	2.18	0.00	*2.18*	0.81	1.10	1.09	−0.37
3	1	1	25.87	13.83	*38.70*	2.43	2.36	*4.79*	0.65	0.54	0.57	+2.76
		2	25.41	11.39	*36.80*	2.49	2.02	*4.51*	0.83	0.63	0.29	+2.47
4	1	1	21.61	9.94	*31.55*	2.49	1.28	*3.73*	0.75	1.03	0.18	+1.77
		2	21.56	6.20	*27.75*	2.97	1.49	*4.46*	0.73	1.17	0.41	+2.67
Mean between studies			26.24	8.72	*34.32*	2.17	1.17	*3.34*	0.63	1.14	0.48	+1.22

Abbreviations: TF, tube-fed; PO, oral; NUUN, non-urea urinary N; Urea N App, urea N appearance; b_N, N balance.

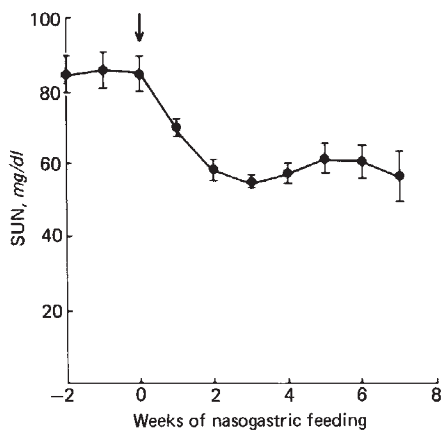

Fig. 1. *Time course of serum urea nitrogen in patients receiving continuous nasogastric alimentation, beginning at time zero.* The *vertical bars* represent 2 × SEM.

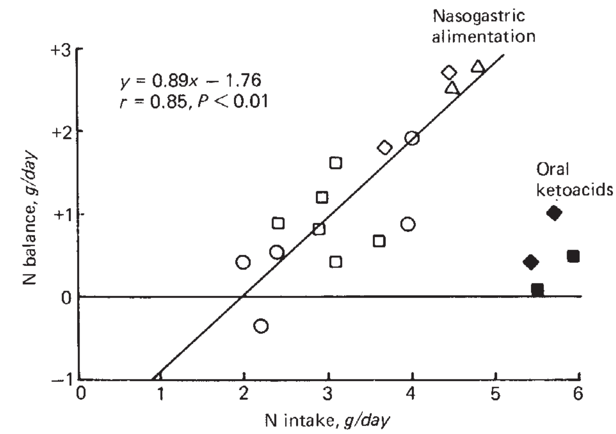

Fig. 2. *Nitrogen balance as a function of nitrogen intake in chronic uremic patients fed by continuous nasogastric infusion.* Each patient is represented by a different symbol, and each point represents one balance period (see Table 2). *Open symbols* are observations during tube-feeding; *solid symbols* are observations on a control regimen. The calculated *linear regression line* is shown. The intersection of the *line* with the *horizontal line* representing zero balance gives an estimate of the nitrogen requirement to achieve balance on this regimen, 2 g/day.

an oral ketoacid/amino acid supplement [3] are also shown. On these regimens, the nitrogen requirement for balance is about 5 g/day. We have reported recently a requirement for nitrogen of about 5 g/day in seven patients receiving a similar ketoacid-containing oral supplement [6].

Plasma amino acid concentrations. Increases occurred in the concentration of essential amino acids, measured at 8 A.M., during tube-feeding (Fig. 3). These changes were statistically significant for leucine, phenylalanine, and lysine. The sum of all eight essential amino acids increased significantly ($P < 0.02$), by 18%. Despite the substantial dose of ornithine, the amino acids of the urea cycle tended to decrease in plasma. The decrease was statistically significant only for citrulline (−28%, $P < 0.01$), an amino acid which is characteristically increased in plasma of patients with chronic renal failure [7]. Tyrosine rose toward normal by 16% ($P < 0.05$) (data not shown).

These changes are of interest because three of these four patients were already receiving a supplement containing essential amino acids plus analogues before the start of tube-feeding, though at a lower dose (16 g/day). No other plasma amino acid concentrations changed significantly except for alloisoleucine in patient 1 (see **Methods**). As noted in **Methods**, R,S-α-keto-β-methylvaleric acid was administered initially instead of isoleucine. Plasma alloisoleucine rose, as it does invariably when this compound is given but more so than usual. Isoleucine levels fell paradoxically (Fig. 4). Similar observations have been made in infants given larger doses of this ketoacid but remain unexplained [8]. When isoleucine itself replaced the ketoacid, plas-

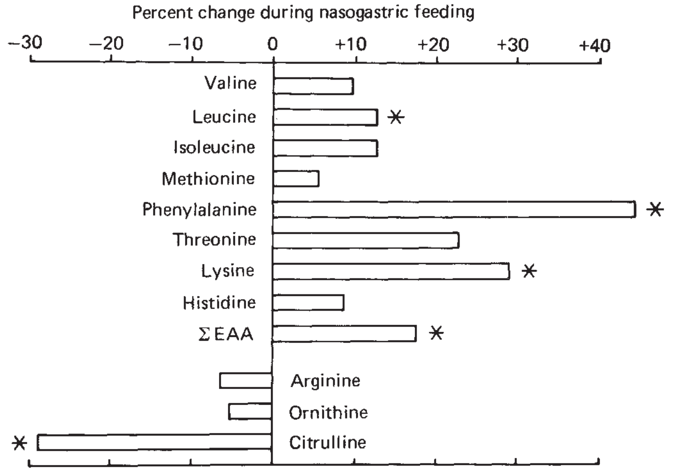

Fig. 3. *Changes in selected plasma amino acids during nasogastric alimentation.* For each study, the difference between the pretreatment value and the average of several values observed during tube feeding was calculated. The mean change was then expressed as a percentage of the initial value and plotted as shown. *Asterisks* indicate statistically significant changes ($P < 0.05$).

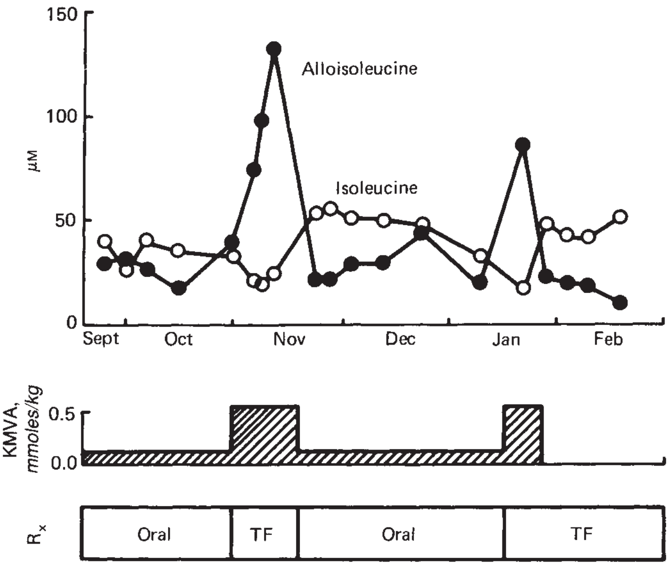

Fig. 4. *Plasma isoleucine and alloisoleucine in patient 1 during a 6-month interval.* Nasogastric alimentation was performed during the periods labelled *TF*. At other times she received a 20 to 25 g protein diet supplemented by an oral ketoacid/amino acid mixture. Racemic KMVA, a mixture of the ketoanalogues of isoleucine and alloisoleucine, was present in the nasogastric infusate at a higher dosage (0.5 mmoles/kg/day) than in the oral supplement (0.2 mmoles/kg/day). Plasma alloisoleucine (normally present only in traces) was 20 to 40 μM during oral supplementation and rose to much higher levels during nasogastric alimentation; concurrently, plasma isoleucine fell during both periods of tube-feeding. KMVA was replaced with L-isoleucine itself in the nasogastric infusate during the last 5 weeks of the second period of tube-feeding; plasma alloisoleucine gradually fell toward trace levels and isoleucine rose promptly to normal levels.

ma isoleucine rose and plasma alloisoleucine gradually fell back to very low levels.

Serum chemical values. Electrolyte concentrations during nasogastric alimentation were essentially normal except for slight hypocalcemia (mean, 8.6 mg/dl) and moderate acidosis (mean carbon dioxide, 18.5 mM). These values were not significantly different from values observed at the start of tube feeding. The anion gap averaged 18.4 mM initially and 18.5 mM during tube-feeding, indicating that no accumulation of keto-acids occurred. Serum phosphate averaged 3.0 mg/dl, significantly lower than the pretreatment mean of 4.2 mg/dl ($P < 0.01$) and was distinctly subnormal in six observation periods. In three of these periods a phosphate supplement (dibasic sodium phosphate, 15 mmoles) was given as a single dose because serum phosphate briefly fell below 2 mg/dl.

None of these patients exhibited protein malnutrition at the start of nasogastric feeding, as indicated by the serum albumin and transferrin levels shown in Table 3. Initial serum albumin averaged 3.8 g/dl before the start of tube-feeding and did not change significantly, during tube feeding. Serum transferrin averaged 304 mg/dl at the start and did not change significantly. Triglycerides (not shown) averaged 140 mg/dl before tube feeding and 165 mg/dl at the end of tube feeding, also a statistically insignificant change. Body weight increased on the average but not significantly.

Effect on rate of progression of renal insufficiency. In three of the four patients, no detectable change in the rate of fall in estimated GFR or reciprocal serum creatinine [9] occurred during tube feeding. In subject 3, the decline of reciprocal serum creatinine concentration ceased during 10 weeks of tube-feeding (Fig. 5). Twenty-four-hour clearances were available only during the first 2 weeks of this time and showed no significant decline. Thereafter, he was treated in the same manner as an outpatient, with the aid of a portable constant infusion pump (Cormed Inc., Middleport, New York). At the end of 10 weeks of tube-feeding, he chose to resume a normal diet. Tube-feeding was discontinued and he soon entered regular dialysis treatment.

Discussion

These results show that continuous intragastric administration of a mixture containing carbohydrate, amino acid analogues, and amino acids can reduce the rate of urinary excretion of waste products and lead to unusually efficient utilization of administered nitrogen in uremic patients, as we have observed in animals [1, 2].

Since there was no evidence for protein malnutrition in these subjects at the start of the studies, the results clearly cannot be attributed to restoration of protein stores in protein-depleted individuals.

No attempt was made in the present study to minimize the urinary output of non-nitrogenous waste products, as we did in rats. The fall in serum phosphate that occurred in the patients presumably reflects an intake too low to compensate for obligatory losses plus the utilization of phosphate for anabolism in conjunction with positive nitrogen balance. A fall in serum phosphate has been demonstrated in uremic patients during parenteral alimentation with phosphate-free solutions [10].

To determine what factors contributed to the low rates of nitrogen output observed in this study, it is instructive to compare the results of this study with three previous studies from this laboratory: two in which essential amino acid and/or

Table 3. Changes in body weight and serum proteins during nasogastric alimentation

Patient no. *age, sex*	Study no., duration *(days)*	GFR *ml/min*		Weight *kg*	Albumin *g/dl*	Transferrin *mg/dl*
1 Female, 78 yr	1 *(17)*	2.9	Initial	72.5	4.1	335
			Final	76.3	3.8	373
			Change	+3.8	−0.3	+38
	2 *(46)*	2.5	Initial	72.9	4.2	374
			Final	75.6	4.0	370
			Change	+2.7	−0.2	−4
	3 *(19)*	1.3	Initial	71.7	3.6	333
			Final	71.1	3.6	358
			Change	−0.6	0.0	+25
2 Female, 62 yr	1 *(58)*	6.5	Initial	53.0	3.4	306
			Final	57.2	3.3	264
			Change	+3.8	−0.1	−42
	2 *(38)*	1.8	Initial	56.7	3.3	181
			Final	54.2	3.7	341
			Change	−2.5	+0.4	+160
3 Male, 48 yr	1 *(70)*	3.6	Initial	66.4	3.6	229
			Final	72.0	4.1	227
			Change	+5.6	+0.5	−2
4 Female, 71 yr	1 *(45)*	1.5	Initial	77.7	4.1	370
			Final	82.1	3.6	280
			Change	+4.4	−0.5	−90
Mean initial value between studies ± SEM					3.8 ±0.1	304 ±28
Mean initial value between patients ± SEM					3.8 ±0.2	298 ±36
Mean change between studies ± SEM				+2.5 ±1.1	0.0 ±0.1	+12 ±29
Mean change between patients ± SEM				+3.2 ±1.1	+0.6 ±0.2	−3 ±31

ketoacid supplements plus glycine were added to virtually protein-free diets [4, 11], and one in which similar supplements were added to a 25-g protein diet [12]. In these other studies, nitrogen intake was greater than in the present study (about 4 g/day), but nitrogen balance was less positive or neutral. Despite the fact that these comparisons are not statistically valid, they offer some clues in the interpretation of the results.

Urea nitrogen appearance is lowest in the present study (1.14 g/day), but was higher during oral intake including glycine without protein [4, 11], and was yet higher in the study in which protein was fed [12]. Thus the low rate of urea nitrogen appearance during nasogastric feeding may be attributable in part to the low dietary intake of whole protein and in part to the nasogastric alimentation itself. Suppression of nocturnal gluconeogenesis may be a factor.

Non-urea urinary nitrogen was the same in the two previous studies whether dietary protein or glycine was given. During nasogastric feeding it is lower by almost 0.3 g/day. Part of this difference is attributable to lower creatinine output in the tube-fed patients, which may, in turn, reflect their more severe renal failure. Recent evidence indicates that creatinine output decreases as renal failure progresses, not because of altered creatinine production, but because of increasing creatinine degradation [13]. Uric acid output was also somewhat lower in tube-fed patients, probably because of lesser purine intake.

Fecal nitrogen was substantially higher in the group receiving protein [12] than in the two groups receiving little protein. The larger fecal residue on higher protein intake is probably responsible.

Since most of the patients in these previous studies were also receiving ketoacids (though at a somewhat lower dosage), it seems unlikely that the lower nitrogen requirement seen here is attributable to ketoacid administration. Further studies will be required to determine whether or not comparable nitrogen conservation can be induced by enteral alimentation for less than 24 hr/day. Feeding this same diet by mouth would be impractical because of its relatively high acidity (pH 2.5).

"Obligatory" excretion rates of nitrogenous waste products have been defined traditionally as those rates observed on a protein-free diet, on the presumption that such a regimen would produce the lowest possible rates. In man, urea nitrogen excretion falls to about 2.5 g/day and total nitrogen excretion to about 4 g/day on a protein-free diet [14]. Both of these rates are approximately twice as high as those observed in the present study. Not all of the difference can be attributed to continuous nasogastric administration of this particular nutrient mixture,

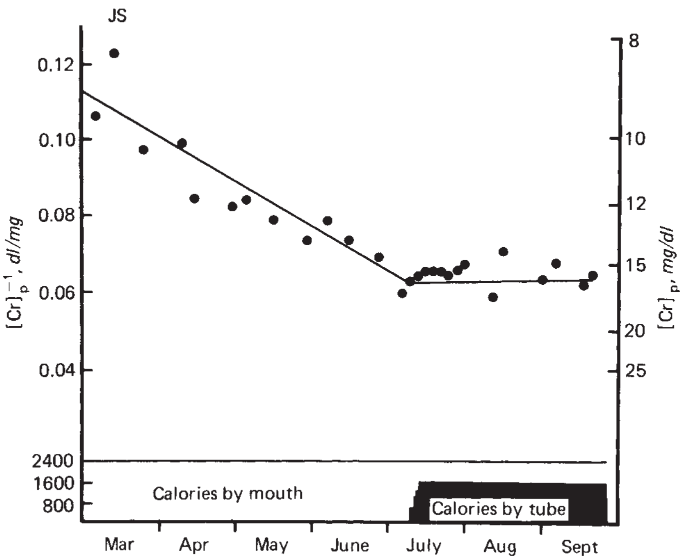

Fig. 5. *Progression of renal insufficiency, as measured by the rate of decline of reciprocal serum creatinine concentration, arrested in one patient during nasogastric alimentation.* Progression was unaffected in the others.

because, as has been documented in many other studies [7], chronic uremia itself tends to reduce excretion rates of creatinine, ammonia, and uric acid, the three main components of non-urea urinary nitrogen. Furthermore, protein restriction plus supplementation with essential amino acids and/or amino acid analogues reduces urea appearance [7].

Guillot et al [15] have recently described results of long-term enteral feeding in children with various forms of renal disease, including three patients with renal failure treated for 4 to 45 months. Protein intake (as casein hydrolysate or whole protein) was 1.5 to 2 g/kg. One patient had acute renal failure and responded well. Another required chronic peritoneal dialysis. Two of the three children grew at normal rates. No attempt was made to minimize the urinary excretion of waste products; instead, the rationale of the study was to ensure an adequate intake of nutrients.

Chronic renal failure in children is difficult to treat and might well be a fruitful area for further investigation of this technique. Portable infusion pumps are available that can permit nearly normal activity. In infants, a gastrostomy route might be preferable. In adults, the practical utility of this technique may be limited to patients who are awaiting the maturation of an arteriovenous fistula or who are temporarily not candidates for dialysis for one reason or another.

Acknowledgments

This study was supported by research grants AM18020 and AM26903 from the National Institutes of Health. Technical assistance was provided by R. Scott, V. Alexander, and D. Mearns. The amino acids and analogues were prepared from commercially available products by S. Hill. The authors thank Grain Processing Corporation, Muscatine, Iowa, for making Mor-Rex available to their study.

Reprint requests to Dr. M. Walser, Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University, School of Medicine, 725 North Wolfe Street, Baltimore, Maryland 21205, USA

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